UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)(KMW)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT JON P. FRYZEK, MPH, PH.D.

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PRELIMINARY STATEMENT

Jon P. Fryzek MPH, Ph.D., an epidemiologist retained by Defendants, submitted a sixty-four page report disputing general causation, *i.e.*, whether the use of Valsartan that is contaminated with NDMA and/or NDEA is capable of causing cancer. Dr. Fryzek was assigned to identify and opine on studies describing the risk of cancer with exposure of valsartan pharmaceutical products and dietary exposure to NDMA or NDEA.

Dr. Fryzek's approach is conclusion driven, without scientific rigor. For example, in his expert report he states sweeping and unsupported opinions, such as "Cohort studies have not demonstrated that NDMA or NDEA in diet are associated with any cancer type." (Expert Report of Jon P. Fryzek, MPH, Ph.D., p. 21 [hereinafter, "Fryzek Report"], Ex. A). However, Dr. Fryzek only cites studies which **do** demonstrate an increased risk of various cancer types when exposed to NDMA in the diet. Similarly, Dr. Fryzek opines "case-control studies assessed as a whole have not found strong evidence that NDMA or NDEA are associated with cancer", but again only cites studies which **do** show strong evidence that NDMA or NDEA are associated with cancer. (Fryzek Report, p. 24-31).

Dr. Fryzek also makes sweeping general statements regarding confounding factors that could result in misleading associations. In deposition, Dr. Fryzek testified that [redacted]. (9/30/2021 Jon P. Fryzek Dep. Tr. 375:5-22 [hereinafter, "Fryzek Dep"], Ex. B). Dr. Fryzek ignored this basis principle, indiscriminately listing numerous potential risk factors that could be confounders for various cancer types, and didn't identify any specific study that didn't properly control for confounders. Furthermore, in both his expert report and deposition, Dr.

Fryzek opined that in order to be a confounder, the variable must be an alternate cause or risk factor for the specific cancer. (Fryzek Report, p. 31; Fryzek Dep 352). However, in his expert report Dr. Fryzek listed numerous variables as confounders that he either doesn't believe are risk factors for the specific cancer or doesn't know if they are risk factors. (Fryzek Report, p. 31-34; Fryzek Dep. 147:20-150:6, 354:14-355:6, 356:14-20, 358:2-361:9, 361:18-366:11, 369:11-373:14, 376:12-15, 378:3-381:3, 407:6-9, 415:17-416:19, 417:13-418:9).

Perhaps most telling, in deposition, Dr. Fryzek discounted the results of the numerous studies he cited in his expert report that show an association between NDMA or NDEA and cancer, **because he** [redacted] (Fryzek Dep 281:1-16). Such pre-conceived notions are unscientific and not based on reliable principles and methods. Therefore, the entire opinion, which is built on unreliable conclusions, should be precluded.

STATEMENT OF FACTS

1. Inconsistencies in Dr. Fryzek's CV, Expert Report, and Invoices

a. Employment History Discrepancies

Dr. Fryzek is an epidemiologist.[1] Dr. Fryzek's credentials and employment are unclear, in part because it is ToxStrategies policy to not list their employment history in their CV. (Fryzek Dep 39:24-40:10). Dr. Fryzek claimed to have given his full employment history in his expert report, which only disclosed that he worked for Amgen and MedImmune from 2006 to 2012. (Fryzek Report, p. 2). Furthermore, Dr. Fryzek testified that [redacted]

[1] After leaving Exponent Dr. Fryzek opened the company EpidStat, which underwent a name change to EpidStrategies after being acquired by ToxStrategies. EpidStat "[redacted]." (Fryzek Dep 49:17-23). ToxStrategies, the parent company of EpidStrategies, and also the employer of defense expert Dr. Britt, was opened by Deborah Proctor after she left Exponent. While at Exponent, Deborah Proctor was [redacted] (Fryzek Dep 402). Dr. Fryzek co-authored chromium studies with Dr. Proctor.

[redacted]. (Fryzek Dep 268:3-14). However, Dr. Fryzek published numerous studies during this timeframe that identified him as an employee of Exponent, to which Dr. Fryzek [redacted]. (Fryzek Dep 271:8-372:7). Instead, Dr. Fryzek suggested we [redacted]. (Fryzek Dep 372:19-373:2). Unlike his expert report or CV, Dr. Fryzek's Linkedin profile actually discloses that he previously worked for both Exponent and the International Epidemiology Institute.[2] (Fryzek Linkedin, Ex. D).

b. Professorship Discrepancies

Interestingly, Dr. Fryzek's Linkedin profile does not indicate that he was ever an assistant professor at the department of medicine at Vanderbilt University, which appears in Dr. Fryzek's CV as an academic appointment from 2000 to 2006. (July Fryzek CV, Ex. E). During Dr. Fryzek's 2005 deposition in the welding rod litigation, he testified that he was only working on grants at Vanderbilt, and that his only assistant professor position was at University Nebraska Medical Center in 1996. (2/8/2005 Jon P Fryzek Dep. Tr. 26:18-28:24, Ex. F). The CV produced with Dr. Fryzek's expert report, which was noted to have been updated in July of 2021, also claimed that Dr. Fryzek was currently an adjunct professor in the department of biostatistics, school of public health, at the University of Pittsburgh, and that he was currently a visiting professor in the department of clinical epidemiology and institute of clinical medicine at Aarhus University in Denmark. An updated CV produced days before Dr. Fryzek's deposition indicated that he was only a professor at Aarhus University until 2016, and the University of Pittsburgh until 2020. (Sept Fryzek CV, Ex. G). However, Dr. Fryzek's updated CV, [redacted], still claims that he was an assistant professor at

[2] The International Epidemiology Institute is known for its industry-commissioned studies (NJ Law Journal, Ex. C).

Vanderbilt University from 2000-2006. (Fryzek Dep 30:22-31:3). Dr. Fryzek is attempting to bolster his credentials by claiming he was an assistant professor at Vanderbilt from 2000 to 2006, but in 2005 he testified under oath that he was merely working on grants. (Ex. F 26:18-28:24).

c. Billing Discrepancies

There are also numerous disturbing inconsistencies with the drafting and billing of the expert report submitted by Dr. Fryzek in this case. His expert report claims that EpidStrategies was paid $412 per hour for Dr. Fryzek's report. (Fryzek Report, p. 3). However, Dr. Fryzek's fee schedule list his hourly rate as $622 per hour. (Fryzek Fee Schedule, Ex. H). Dr. Fryzek was "[redacted]", but like his CV, Dr. Fryzek claimed his fee schedule was [redacted]. (Fryzek Dep 18:8-15). Additionally, Dr. Fryzek was "[redacted]. (Fryzek Dep 19:2-5).

d. Expert Report Authorship Discrepancies

A majority of Dr. Fryzek's expert report was drafted by people other than Dr. Fryzek, but it is unclear who all of those people are.[3] 123 hours were billed by Janice Lansita in relation to Dr. Fryzek's expert report, with 122.5 of those hours being billed in 2021. (Invoices, Ex. I). Oddly, Janice Lansita's Linkedin profile indicates that she left ToxStrategies in July of 2020. (Janice Lansita Linkedin, Ex. J). In deposition, Dr. Fryzek admitted that Janice Lansita's billing "[redacted]." (Fryzek Dep 55:7-13). ToxStrategies' and EpidStrategies' employees Mina Suh, Naimisha Movva, and Sarah Cohen billed a combined 144.5 hours for Dr. Fryzek's expert report. Another 117.1 hours were billed by "Professional Support Staff." When asked in deposition who the professional support staff was, Dr. Fryzek testified "[redacted]." (Fryzek Dep 54:4-8). Furthermore, Dr.

[3] 491.85 hours were billed for Dr. Fryzek's report, with Dr. Fryzek billing 107.25 of those hours (Invoices, Ex. I).

Fryzek testified in deposition that [redacted], who does not appear anywhere in the invoices produced. (Fryzek Dep 391:3-5).

e. Similar Discrepancies in Previous Welding Rod MDL

The significant discrepancies in Dr. Fryzek's CV, invoices, expert report, Linkedin profile, and prior depositions are even more concerning in light of his previous work on the welding rod MDL in the Eastern District of Ohio under Judge Kathleen O'Malley.[4] In regard to two welding rod studies published by Dr. Fryzek, Judge O'Malley noted that "Since the beginning of this MDL, this Court has repeatedly addressed a number of issues related to two epidemiological studies known as the Danish and Swedish Studies. Defendants provided funding for both studies, and both studies concluded there was no link between welding and parkinsonism. Recitation of the full and complicated background of the issues related to the Danish and Swedish Studies is beyond the scope of this Order; it suffices to say there were discovery issues related to the two studies serious enough to give the Court reason to exclude any reference to them at any MDL trial." (Judge O'Malley Evidentiary Order, Ex. K; Fryzek Dep 174:10-175:1). Judge O'Malley ordered full disclosure of payments by any of the parties to the researchers, which revealed "the welding companies pay more than $12.5 million to 25 organizations and 33 researchers, virtually all of whom have published papers dismissing the connection between welding fumes and workers' ailments." (Ex. C). The court documents further revealed that "John Fryzek, who works for Maryland's International Epidemiology Institute—known for its 'industry-commissioned studies'—was paid $971,000 from welding defendants." (Ex. C). When confronted about the above in his recent deposition, Dr. Fryzek claimed [redacted]. (Fryzek Dep 182:1-185:6). Dr. Fryzek's

[4] 1:03-cv-17000-KMO.

testimony regarding payments made in the welding rod litigation is strikingly similar to the testimony Dr. Fryzek gave in regard to [redacted]. As a result of not knowing or being able to question those most involved in the drafting of the report submitted by Dr. Fryzek, the methodology by which the opinions contained within the expert report submitted by Dr. Fryzek were reached was not able to be adequately explored or explained, and therefore the opinions contained with the expert report submitted by Dr. Fryzek should be excluded.

2. Dr. Fryzek's Flawed Literature Selection Methodology

Dr. Fryzek claimed to have conducted a systemic literature review to identify relevant literature regarding the risks of cancer with exposure to valsartan, NDMA or NDEA. (Fryzek Report, p. 9). However, Dr. Fryzek would not have been able to adequately search for or identify what literature was actually relevant, as evidenced by Dr. Fryzek testifying "[redacted]" when shown a study on dimethylnitrosamine and asked if [redacted]. (Fryzek Dep 156:1-4). Dimethylnitrosamine is another word for N-Nitrosodimethylamine, or NDMA, the main carcinogen at issue in this litigation and in the expert report submitted by Dr. Fryzek.

Dr. Fryzek's literature search resulted in 1,884 studies, which he narrowed to only 25 studies. (Fryzek Report, p. 9). Two of the 25 studies selected for his expert report are on ranitidine, a drug not at issue in this litigation or within the search criteria put forth by Dr. Fryzek. *Id*. Of the 1,884 studies resulting from Dr. Fryzek's literature search, the full text of only 117 articles were reviewed. *Id*. Dr. Fryzek's materials considered do not indicate the 1,775 articles that were excluded from his expert report. When asked in deposition [redacted], Dr. Fryzek responded "[redacted]." (Fryzek Dep 115:19-23). There is also no indication why any specific study was excluded. Furthermore, Dr.

Fryzek eliminated 14 studies because they were "reviews or meta-analyses" but included one meta-analysis study without any justification for its inclusion. (Fryzek Report, p. 10, 28). Dr. Fryzek's methodology used to select the literature within the expert report he submitted is not clear, he does not follow the methodology laid out in his report, and he cherry-picks studies to include, while excluding or not even considering studies that go against his opinions.

3. Dr. Fryzek's Flawed Literature Analysis

a. Studies that Describe the Risk of Cancer with Use of Valsartan

Dr. Fryzek opines "valsartan and valsartan-containing prescriptions are NOT associated with cancer" based on "studies that describe the risk of cancer with use of ***valsartan-containing prescription***." (Fryzek Report, p. 13 (emphasis added)). However, two of the five studies he pointed to are on ranitidine, not valsartan. In regard to the NDMA ranitidine studies that Dr. Fryzek reviewed but didn't include in his report, when asked if [redacted], Dr. Fryzek testified "[redacted]." (Fryzek Dep 127:3-20). When asked [redacted], Dr. Fryzek replied "[redacted]." (Fryzek Dep 122:11-13). When asked if [redacted], Dr. Fryzek again replied "[redacted]". (Fryzek Dep 124:9-12). Furthermore, when questioned if [redacted], Dr. Fryzek testified "[redacted]." (Fryzek Dep 106:6-9). **However, when later asked [redacted], Dr. Fryzek testified "[redacted]."** (Fryzek Dep 165:13-166:4).

Dr. Fryzek previously published his opinion that "[redacted]." (Fryzek Dep 384:7-11). However, Dr. Fryzek testified that

he [redacted]. (Fryzek Dep 421:4-422:1). The human occupational studies that show an increased risk of numerous types of cancer due to NDMA exposure should have been captured by Dr. Fryzek's search terms, met his inclusion criteria, and did not meet his exclusion criteria. (Fryzek Report, p. 9-10). Thus, Dr. Fryzek diverged from his stated methodology and excluded the human occupational studies that demonstrate an increased risk of cancer due to NDMA exposure.

b. NDMA or NDEA Diet Cohort Studies

Dr. Fryzek relied on six cohort studies as the basis for his opinion that "cohort studies have not demonstrated that NDMA or NDEA in diet are associated with ***any*** cancer type." (Fryzek Report, p. 21 (emphasis added)). However, the first study Dr. Fryzek cited notes "an increased risk of colorectal cancer was observed in the highest quartile of NDMA intake compared to the lowest." (Fryzek Report, p. 21). The second study Dr. Fryzek cited found that "non-cardia stomach cancer had increased risk with tertiles of NDMA, but none were statistically significant." (Fryzek Report, p. 21). The third study Dr. Fryzek cited concluded "there was a trend of increasing risk of stomach cancer with increasing NDMA intake and ***a dose-response trend was observed***" (Fryzek Report, p. 22 (emphasis added)). The fourth study Dr. Fryzek cited found a non-statistically significant increased risk for bladder cancer at the highest level of NDMA intake. (Fryzek Report, p. 22). The fifth study Dr. Fryzek cited found that "when NDMA intake was analyzed as a continuous variable, there was a small statistically significant increased cancer risk per unit increase in NDMA intake" (Fryzek Report, p. 22-23). Finally, the sixth study cited by Dr. Fryzek concluded that when "analyzed as a continuous variable, esophageal squamous cell cancer risk was increased per unit increase of NDMA for both men and women."[5] (Fryzek Report, p. 23).

[5] Studies cited by Dr. Fryzek show an association with NDMA and cancer to estimated exposure levels of less than 96 nanograms per day, which is less than the amount of NDMA the FDA currently allows in valsartan.

Every cohort study cited by Dr. Fryzek demonstrated an increased risk of cancer with increasing NDMA exposure. (Fryzek Report, p. 21 – 23). Dr. Fryzek's opinion that "cohort studies have not demonstrated that NDMA or NDEA in diet are associated with any cancer type" is not supported by any of the literature he cited to support his opinion.

c. NDMA or NDMA Case-Control Studies

i. Lung Cancer

Dr. Fryzek cited three case-control studies related to NDMA and lung cancer. (Fryzek Report, p. 24-25). The first study cited by Dr. Fryzek states that "an association between NDMA and risk of lung cancer was observed for men in the highest two categories of NDMA intake with a ***strong dose-response trend*** after adjusting for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake (emphasis added)."[6] (Fryzek Report, p. 24). The second study cited by Dr. Fryzek concluded that "an association was seen between NDMA intake and lung cancer at the third and highest quartiles of intake, controlling for age, sex, residence, urban/rural status, family history of lung cancer, BMI, pack-years, and total energy intake." (Fryzek Report, p. 24-25). Dr. Fryzek then cites Loh 2011 to support the proposition that NDMA doesn't increase the risk of lung cancer. (Fryzek Report, p. 25). However, Loh detected statistically significant increases in numerous types of cancer, and a non-statistically significant increase for lung cancer. (Loh 2011, Ex. L). Dr. Fryzek testified that he discounted the studies that found a positive association because the lowest levels of exposure didn't show an increased risk. (Fryzek Dep 280:23-281:19). Dr. Fryzek provided no explanation for why he concluded higher levels of NDMA can't cause cancer based solely on lower levels of NDMA not showing evidence of an increased rate of cancer in the same study. When the rate of a side effect increases

[6] Study showed up to a 530% increased risk of lung cancer due to NDMA exposure (Fryzek Dep 274:5-8).

as the dose of an exposure increases, it is known as a dose response. In trying to determine if epidemiologic associations are causal, Sir Austin Bradford Hill wrote that "if a dose response is seen, it is more likely that the association is causal." (Applying the Bradford Hill Criteria, Ex. M). Dr. Fryzek's methodology is at odds with Bradford Hill, a widely accepted guideline since 1965 for investigating causality in epidemiological studies.

All three case-control NDMA lung cancer studies cited by Dr. Fryzek found varying degrees of increased risk of lung cancer with NDMA exposure, and he failed to exclude the significance of those studies based on any scientific analysis. (Fryzek Report, p. 24-25). Therefore, Dr. Fryzek should be precluded from offering the opinion that case-control studies have not found evidence that NDMA is associated with lung cancer.

ii. Stomach Cancer

Dr. Fryzek cited to eight case-control studies related to NDMA exposure and stomach cancer, including one meta-analysis. (Fryzek Report, p. 25-29). It is unclear why Dr. Fryzek included the meta-analysis, as he eliminated 14 other studies "because they were reviews or meta-analyses." (Fryzek Report, p. 10). The first study cited by Dr. Fryzek found that "stomach cancer risk was increased with increasing smoked meat intake, a food high in NDMA, after adjusting for other food groups, total food consumption and ethnicity." (Fryzek Report, p. 25-26). The second study Dr. Fryzek cited found "an increasing risk of stomach cancer was seen with increasing NDMA intake" (Fryzek Report, p. 26). The third study cited by Dr. Fryzek noted that when "using the fully adjusted model, there was an increased risk of stomach cancer at the highest intake of NDMA" (Fryzek Report, p. 26). The fourth study cited by Dr. Fryzek found that "there was a 7-fold risk of stomach cancer with the highest NDMA intake" (Fryzek Report, p. 27). The fifth study cited by Dr. Fryzek concluded that when "measured continuously and included in a single model

with other food items and micronutrients, increasing NDMA intake was associated with increased risk of stomach cancer." (Fryzek Report, p. 27). The sixth study cited by Dr. Fryzek determined an odds ratio of 1.5 (50% increased risk) between NDMA intake and gastric cancer, though the results were slightly below statistical significance. (Fryzek Report, p. 27-28). The seventh study cited by Dr. Fryzek noted that "dietary intake of NDMA was associated with a non-statistically significant increased risk of gastric cancer, after adjusting for various potential confounders. (Fryzek Report, p. 28). Finally, Dr. Fryzek cited to a meta-analysis that also found an increased risk of stomach cancer due to NDMA. (Fryzek Report, p. 28-29).

When confronted in deposition with the fact that all of the case-control studies that he cited to support his opinion that NDMA is not associated with an increased risk of stomach cancer actually do show an increased risk of stomach cancer, Dr. Fryzek quipped "[redacted]." (Fryzek Dep 338:11-13). The studies shown to Dr. Fryzek during his deposition that demonstrated an increased risk of stomach cancer due to NDMA were not cherry-picked by plaintiffs' counsel, they were the precise studies that were included as the basis of his opinion in the expert report he submitted. **Every case-control study that Dr. Fryzek cited related to NDMA and stomach cancer found that NDMA increases the risk of stomach cancer, and he failed to scientifically exclude this data**. Therefore, Dr. Fryzek should be precluded from offering the opinion that case-control studies do not demonstrate an increased risk of stomach cancer due to NDMA exposure.

iii. Upper Aerodigestive Cancers (Larynx, Esophagus, Oral Cavity)

Dr. Fryzek cited two case-control studies related to NDMA and the risk of upper aerodigestive cancers. (Fryzek Report, p. 29-30). The first study cited by Dr. Fryzek found that "cancer of the oral cavity was increased with NDMA intake but was only statistically significant

at the highest levels." (Fryzek Report, p. 29). The second study cited by Dr. Fryzek noted that "NDMA was found to be associated with ESCC [esophageal squamous cell carcinoma], after adjusting for age, gender, residence, education, BMI, smoking, alcohol use, mate drinking, total energy intake, total vegetables, fruits, grains, non-meat fatty foods, and different types of meat." (Fryzek Report, p. 30).

When confronted with this data in his deposition, he simply conceded this: "[redacted]?" Dr. Fryzek answered, "[redacted]." (Fryzek Dep 344:14-17). When pushed further on how he can opine that the case-control studies do not any show evidence of an increased risk of cancer, Dr. Fryzek replied "[redacted]." However, the lowest confidence interval was actually 2.12 (212% increased risk), to which Dr. Fryzek conceded "[redacted]." (Fryzek Dep 343:2-13). **This was symptomatic of Dr. Fryzek's approach – he rendered conclusions untethered to the evidence he claimed to be relying on**. Every case-control study that Dr. Fryzek cited related to NDMA and upper aerodigestive cancers found that NDMA increases the risk of upper aerodigestive cancer. Therefore, Dr. Fryzek should be precluded from offering the opinion that case-control studies do not demonstrate an increased risk of upper aerodigestive cancers due to NDMA exposure.

iv. Colorectal Cancer

Dr. Fryzek cited a single case-control study related to NDMA and colorectal cancer. (Fryzek Report, p. 30). The lowest level of NDMA exposure in the study was 30 nanograms (0.03 µg) per day and the highest level of exposure was 2,290 nanograms (2.29 µg) per day.[7] (Fryzek Report, p. 30). The study concluded that "intake of NDMA was found to be associated with risk

[7] The FDA currently allows valsartan with less than 96 nanograms of NDMA to be sold. Prior to the recall, many valsartan pills contained hundreds up to tens of thousands nanograms of NDMA.

of colorectal cancer at the highest level of intake, increased risk were reported for the lower quintiles of exposure, but none were statistically significant." (Fryzek Report, p. 30). In deposition, Dr. Fryzek conceded that [redacted]. (Fryzek Dep 348:3-9). Therefore, Dr. Fryzek should be precluded from opining that case-control studies do not demonstrate an increased risk of colorectal cancer due to NDMA exposure.

v. Pancreatic Cancer

Dr. Fryzek cites a single case-control study related to NDMA/NDEA exposure and pancreatic cancer. (Fryzek Report, p. 31). The study found that "plant sources of NDMA were associated with a statistically significant increased risk at high levels of intake compared to the lowest levels" and that "increasing intake of NDEA, however, increased the risk of pancreas cancer at all quartiles of intake compared to the lowest level". (Fryzek Report, p. 31). Thus, the only case-control study cited by Dr. Fryzek found that both NDMA and NDEA increase the risk of pancreatic cancer. Therefore, Dr. Fryzek should be precluded from offering the opinion that case-control studies do not demonstrate an increased risk of pancreatic cancer due to NDMA or NDEA exposure.

4. Opinions Regarding Confounding Factors

a. Failure to Identify Specific Studies that did Not Account for Confounders

Dr. Fryzek states in his report that confounders are variables that affect both exposure and outcome, and are possible alternative causes for the cancer. (Fryzek Report, p. 31). Furthermore, he equates confounders to risk factors in his report. (Fryzek Report, p. 34). When asked if potential risk factors would have a smaller confounding effect than known risk factors, Dr. Fryzek testified "[redacted]." (Fryzek Dep 374:6-9). Additionally, Dr. Fryzek testified that "[redacted]

[redacted]." (Fryzek Dep 376:9-11 (emphasis added)). Dr. Fryzek testified that [redacted]. (Fryzek Dep 375:17-22). Thus, Dr. Fryzek's methodology, which failed to differentiate the context within which a factor could be a confounder, is inconsistent, and therefore unreliable. Despite this, Dr. Fryzek only discusses confounders generally in his expert report. (Fryzek Report, p. 31-34). Dr. Fryzek did not identify specific studies that failed to account for specific confounders, or the magnitude of impact that the confounder could have potentially had on the specific study. (Fryzek Report, p. 31-34). As such, Dr. Fryzek should be precluded from offering opinions regarding confounding factors on any specific study since he is just throwing up a speculative argument in general, to muddy the waters.

b. Listed NDMA Containing Exposures as Cancer Risk Factors

Dr. Fryzek listed intake of salt-preserved fish and working in the rubber industry as well-confirmed risk factors for the development of cancer, but did not provide a reason for why either increases the risk of cancer. (Fryzek Report, p. 33). In deposition, Dr. Fryzek initially [redacted]s. (Fryzek Dep 225:21-226:13). However, once confronted with his opinion that salt-preserved fish are a well-confirmed risk factor for cancer, Dr. Fryzek suddenly [redacted]. (Fryzek Dep 405:6-406:15). Additionally, Dr. Fryzek also [redacted]. (Fryzek Dep 421:4-7).

c. Listed Cancer Risk Factors Contrary to His Prior Publications

Dr. Fryzek also listed numerous confounders for various cancer types, but has previously published articles funded by industry saying that such exposures do not increase the risk of cancer. For instance, Dr. Fryzek list beryllium as a probable risk factor for lung cancer. (Fryzek Report, p. 33). However, in 2011 while working for Exponent, Dr. Fryzek submitted a study that was published in 2012, which concluded "the available evidence does not support a conclusion that a causal association has been established between occupational exposure to beryllium and the risk of cancer." (Occupational Exposure to Beryllium, Ex. N). For the sake of brevity, one additional example is that chromium was listed as a probable risk factor for lung cancer in the report submitted by Dr Fryzek, yet in deposition he testified [redacted]" when asked if chromium is a risk factor for cancer. (Fryzek Dep 379:5-14). Furthermore, Pacific Gas and Electric Company hired Dr. Fryzek and the International Epidemiology Institute after getting sued for chromium exposure in California,[8] and Dr. Fryzek then published a study finding no evidence of a cancer hazard to the residents living near the contamination. (Cancer Mortality Chromium Exposure, Ex. O; Fryzek Dep 380:16-383:22). Dr. Fryzek's opinions are unreliable, as they change based on who has hired him, and therefore his opinions should be excluded.

5. Disclaimed Opinions Regarding Risk Assessment

Dr. Fryzek testified that [redacted]. (Fryzek Dep 125:17-19). However, [redacted], the FDA's NDMA risk assessment appears in the report submitted by Dr. Fryzek, but in a lighter colored font than the rest of the report he submitted. (Fryzek Report, p. 49; Fryzek Dep 432:7-22). Even though the FDA acknowledges that NDMA and NDEA can

[8] The lawsuit was eventually made into a movie called *Erin Brockovich*. (Fryzek Dep. 381:10-382:22).

increase the risk of cancer, Dr. Fryzek testified that [redacted]" and that the [redacted]. (Fryzek Dep 124:17-24). When shown during his deposition that the FDA's NDMA risk assessment was within the report he submitted, Dr. Fryzek responded "[redacted]." (Fryzek Dep 433:3-8 (emphasis added)). Therefore, Dr. Fryzek should be prohibited from offering any risk assessment opinions or critiques.

6. Ipse Dixit Opinions

Dr. Fryzek opines that "If NDMA exposure is a trigger for cancer growth and development, cancer incidence would be far higher in the general population and the diet studies would show much stronger effects with the daily exposure humans receive from NDMA." (Fryzek Report, p. 56). However, in deposition Dr. Fryzek admitted that he [redacted]. (Fryzek Dep 139:11-16). When asked how he could give the above opinion without knowing the [redacted], Dr. Fryzek answered "[redacted]." (Fryzek Dep 139: 17-22). Furthermore, when asked if the inverse would be true—if we didn't have NDMA in our diet and we weren't exposed to NDMA at all, would we expect lower cancer rates? Dr. Fryzek [redacted]." (Fryzek Dep 139:15-19). Finally, when asked how much NDMA a human is exposed to daily through their diet, Dr. Fryzek [redacted]." (Fryzek Dep 139:20-22). Dr. Fryzek's opinion is the epitome of *ipse dixit*—If NDMA is carcinogenic, more people would be getting cancer, because I said so.

Dr. Fryzek also chastised plaintiffs' experts, opining that "it is absurd to suggest that workers in [Hidajat] had similar levels of exposure to NDMA as valsartan users and that any findings of this study are applicable.[9] (Fryzek Report, p. 52). However, in deposition Dr. Fryzek [redacted]. (Fryzek Dep 441:10-15). Dr. Fryzek attempted to justify his opinion by [redacted].[10] But when asked if a substance is a carcinogen via one route, isn't it a known carcinogen, Dr. Fryzek answered "[redacted]." (Fryzek Dep 444:4-9).

7. Regulatory and Governmental Critiques of Dr. Fryzek's Work

Recently, the office of attorney general for the commonwealth of Pennsylvania opened a statewide investigating grand jury "based on evidence that private companies engaged in unconventional oil and gas activities [fracking] have committed criminal violations of Pennsylvania's environmental laws." (Statewide Investigating Grand Jury, Ex. P at 9). Dr. Fryzek previously published studies with funding from America's Natural Gas Alliance that found no increased risk of childhood cancer incidence in Pennsylvania counties with hydraulic fracturing sites. (Childhood Cancer Hydraulic Fracturing, Ex. Q). The grand jury investigation noted that in 2019 the Department of Health and the State of Colorado published a study titled "A Systemic Review of the Epidemiologic Literature Assessing Health Outcomes in Populations Living near Oil and Natural Gas Operations: Study Quality and Future Recommendations." (Ex. P at 178). The Department of Health and the State of Colorado specifically called out Dr. Fryzek for incorrectly interpreting results and for cherry-picking the data that he utilized. (Ex. P at 218).

[9] Dr. Fryzek inexplicitly excluded Hidajat from his literature results.
[10] Dr. Fryzek criticized Dr. Madigan for assuming the NDMA exposure in Hidajat was respiratory (Fryzek Report, p. 54).

Dr. Fryzek's methodology and opinions have been found to be unreliable by numerous sources, and on numerous occasions. In deposition, Dr. Fryzek testified that he [redacted]. (Fryzek Dep 117:13-24). As such, Dr. Fryzek should be precluded from offering opinions related to general causation, and his report should be excluded in its entirety.

I. THE *DAUBERT* STANDARD

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. "As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be more informative than confusing." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 800 (2017). Additionally, "[b]oth an expert's methodology and the application of that methodology must be reviewed for reliability." *Zoloft*, 858 F.3d at 791. The "specific way an expert conducts such an analysis must be reliable; '**all of the relevant evidence must be gathered**, and **the assessment or weighing of that evidence must not be arbitrary**, but must itself be **based on methods of science.**'" *Id.* at 796.

The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Zoloft*, 858 F.3d at 745. Judges

within this Circuit also consider how and when the methodology is used outside of litigation. *Paoli*, 35 F.3d at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 594 (D.N.J.2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation (*see Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (*see General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) whether the expert has adequately accounted for alternative explanations (*see Claar v. Burlington, N.R.R.,* 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95. To this end, the Third Circuit has affirmed the exclusion of expert testimony that "failed to consistently apply the scientific methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion." *Zoloft*, 858 F.3d at 792.

II. DR. FRYZEK'S OPINONS SHOULD BE PRECLUDED PURSUANT TO DAUBERT

Dr. Fryzek's opinion on general causation, the question he sought to answer, rests on his analysis of the 25 studies he decided to include from his literature review of 1,884 studies. "Both an expert's methodology and **the application of that methodology must be reviewed for**

reliability." *In Re: Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 792 (3rd Cir. 2017), emphasis added. To begin with, Dr. Fryzek included studies that did not meet the inclusion criteria laid out in his expert report, and also included studies that met the exclusion criteria laid out in his expert report.

In granting a motion to preclude an expert under *Daubert*, this Court has observed:

> [C]ourts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered…. Mere assumptions, without causal evidence or methodological analysis may be inadmissible.... Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard.

Player v. Motiva Enterprises LLC, 2006 WL 166452, at *6-7 (D.N.J. January 20, 2006) (citations omitted). In *Player*, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. The Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8. As previously set forth in detail in the sections discussing Dr. Fryzek's flawed literature review methodology and analysis, Dr. Fryzek did not follow his own literature inclusion and exclusion criteria. *See* discussion *supra* p. 10-12. For instance, Dr. Fryzek excluded 14 studies because they were reviews or meta-analyses but still included one meta-analysis in his report. (Fryzek Report, p. 10, 28). Dr. Fryzek additionally included two studies on ranitidine, which did not meet his exclusion criteria, and he [redacted]. (Fryzek Report, p. 10, 13, 17; Fryzek Dep 127:3-20). Furthermore, Dr. Fryzek excluded human occupational studies that demonstrate an increased risk of cancer due to NDMA

exposure, even though the studies would have been identified by his literature search terms, met his inclusion criteria, and did not meet his exclusion criteria. (Fryzek Report, p. 9-10). By ignoring the literature inclusion and exclusion criteria laid out in his expert report, Dr. Fryzek in essence followed no methodology.

In addition to these methodological failings, Dr. Fryzek was [redacted]. (Fryzek Dep 103:9-24, 105:19-106:9, 107:3-6, 433:23-434:9, 440:13-15, 441:10-15). This lack of foundational knowledge renders his opinions untethered to facts, and therefore inadmissible net opinions. *See Buckelew v. Grossbard*, 87 N.J. at 524. Moreover, this lack of knowledge and experience should result in greater scrutiny of the method actually applied by the expert. *See Elcock*, 233 F.3d at 747 (quoting *Paoli*, 35 F.3d at 742, n.8). Dr. Fryzek also formed his opinions in this case solely for the purposes of litigation, and [redacted]. (Fryzek Dep 156:1-19, 421:4-422:1). Furthermore, over the last two decades Dr. Fryzek has been funded by a plethora of corporations and industry groups to publish studies refuting various factors as being able to increase the risk of cancer, but now wants to point his finger at those same factors as alternative causes for cancer now that it benefits his current client. *See* discussion *Supra* p. 19. This should all factor into the Court's determination of reliability:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes

> of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir. 1995). Expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's scientific research or technical work should be viewed with some caution. *Magistrini*, 180 F. Supp. 2d at 594 (D.N.J.2002).

Dr. Fryzek's flawed methodology dooms his opinions disputing general causation of the cancers claimed by the Plaintiffs here. In order for Dr. Fryzek's opinions to be admissible, "the process or technique used in formulating the opinion [must be] ... reliable," and the principles and methods employed by the expert [must be] . . . applied reliably to the facts of the case. *Pineda, 520 F.3d* at 247 (citing *Paoli,* 35 F.3d at 742); *see also* Fed. R. Evid. 702, Advisory Committee's Note. The failure by Dr. Fryzek to [redacted], is fatal to his methodology. (Fryzek Dep 100:5-9, 101:19-23, 103:9-24, 105:19-106:9, 107:3-6, 122:11-13, 124:9-12, 247:15-18, 329:3-15, 406:4-15, 433:23-434:9, 438:15-16, 440:13-15, 441:10-15). It is impossible for Dr. Fryzek to reliably provide an opinion comparing the level of NDMA exposure via valsartan to other sources of NDMA exposure, when Dr. Fryzek [redacted].

Furthermore, Dr. Fryzek's opinion in his report claiming that cohort studies and case-control studies on NDMA or NDEA have not demonstrated an association with any cancer type, is not only inconsistent with the prevailing scientific consensus, but also counter to ***all*** the studies cited by Dr. Fryzek in support of his opinion, thus the method that yielded the opinion in the report should be scrutinized closely. *See In re Zoloft Products Liability Litigation,* 176 F. Supp. 3d 449,

460-61 (E.D. Pa. 2016), (citing *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) ("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable.")). All the literature cited by Dr. Fryzek, which he notes in his expert report are relevant, refute the opinions that he is attempting to offer in this litigation. *See* discussion *Supra* p. 12-17.

Indeed, in order to ensure that the methodology is truly a methodology, rather than a mere conclusion-oriented selection process, there must be a scientific method that is used and explained. *Magistrini*, 180 F. Supp. 2d at 607. An expert's failure to comment on the potential weaknesses of the studies upon which an expert relies nor to acceptably explain why he did not accord more weight to other studies that did not align with his conclusions may render the opinion unreliable. *Magistrini*, 180 F. Supp. 2d at 584. Dr. Fryzek failed to do so here, [redacted]. (Fryzek Dep 338:5-339:20).

To reach an opinion on general causation in this case, Dr. Fryzek simply made a naked assertion that the studies he cited supported the position of his client. This is the epitome of arbitrary and runs counter to even the most basic percepts of the scientific method. As the gatekeeper of the jury, this Court should consequently exclude Dr. Fryzek's opinions. *See Zoloft*, at 796, 800. [redacted], and he should not be allowed to testify at trial in the litigation. (Fryzek Dep 187:14).

CONCLUSION

For the foregoing reasons, Dr. Fryzek should be precluded from offering his opinions related to general causation.

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Respectfully,

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